weight or other response. Sugared foods were then entirely excluded from the diet, and the usual response occurred in these cases. The data, so far, certainly do not suggest that highly processed sugar is any better than the crude substance.

7. *Age Factor*.—The relationship between refractory infective conditions, metabolic state, and response to oestrogens is further complicated by an age factor, the threefold disturbance being comparatively less common in infecund women under 30: its incidence seems to rise, like that of obesity in general, during the fourth decade of life. The complex here discussed represents one of the modes by which fecundity declines.

8. *General Notes*.—The use of sugar-free diets is not suggested for cases of obesity in general, for our experience is entirely limited to infecund women in the reproductive phase of life. Also, the syndrome involving refractory genital infection, overweight, and lack of response to hormones may be determined by specific and topical conditions such as the prevailing food restrictions combined with the demand made upon the physical resources of women in this country during the past years. Nevertheless, we are submitting our findings because the dietary measures described have been of great practical assistance to us in our work; and in recent months dietary measures have been employed in every suitable case from the very beginning of treatment in order to save time.

Summary

Refractory cervical block is a common cause of infecundity in overweight women aged 30 to 40. It tends to respond to treatment by antibiotics and oestrogens if loss of weight is first procured by dietary measures. Suitable diets which do not interfere with the routine of the subjects are described. Their main characteristic is the exclusion of sucrose, with concomitant increase in other foods chosen to produce a diet adequate for maintenance and reproduction within the limitations imposed by rationing.

The bacteriological investigations for the present series were carried out by Dr. R. C. Matson, pathologist, Royal Surrey County Hospital, Guildford, to whom our thanks are due for help and advice on many occasions. His routine procedure is summarized in the footnote. We are also indebted to Mr. A. L. Bacharach for discussion of nutritional aspects of this investigation, and to the Scientific Adviser, Ministry of Food, for supplying crude cane-sugar for issue to subjects.

REFERENCES

- Aschner, B. (1924). *Die Konstitution der Frau*. Munich.
Barton, M., and Wiesner, B. P. (1945). *Irish J. med. Sci.*, 6th ser., 567.
— (1946). *British Medical Journal*, 2, 606.
Bauer, A. (1934). *Ernährungsbehandlung in der Gynäkologie und Geburtshilfe*. Vienna.
Cannon, P. R. (1942). *J. Immunol.*, 44, 107.
Clift, A. F. (1945). *Proc. R. Soc. Med.*, 39, 1.
Duncan, G. G. (1947). *Diseases of Metabolism*. Philadelphia and London.
Guggisberg, H. (1946). *Lehrbuch der Gynaekologie*. Basle.
Hite, K. E., Hasseltine, H. C., and Goldstein, L. (1947). *Amer. J. Obstet. Gynec.*, 53, 233.
Hunt, T. C. (1931). *Lancet*, 2, 872.
Koehler, A. E., and Allen, S. E. (1934). *J. Nutrit.*, 8, 377.
— Rapp, I., and Hill, E. (1935). *Ibid.*, 9, 715.
Kuester, E. (1929). *Handbuch der pathogenen Mikroorganismen* edited by Kolle, Kraus, and Uhlenhuth, 6, part I, 356. Jena.
Lamar, J. K., Shettles, L. B., and Delfs, E. (1940). *Amer. J. Physiol.*, 129, 234.
McCann, F. J. (1934). *The Treatment of Common Female Ailments*. London.
Palmer, E., and Palmer, R. (1945). *Gynec. Obstet.*, 44, 198.
Roberts, C. Lane, Sharman, A., Walker, K., Wiesner, B. P., and Barton, M. (1948). *Sterility and Impaired Fertility*. London.
Robinson, C. S., and Duncan, C. W. (1931). *J. biol. Chem.*, 92, 435.
— and Gilliland, H. L. (1937). *Proc. soc. exp. Biol. Med.*, N.Y., 37, 336.
Rojas, J., Schweigert, B. S., and Rupel, I. W. (1948). *J. Dairy Sci.*, 31, 81.
Siegler, S. L. (1944). *Fertility in Women*. London.
Viergiver, E., and Pommerenke, W. T. (1946). *Amer. J. Obstet. Gynec.*, 51, 192.
Webb, B. H., and Whittier, E. O. (1948). *J. Dairy Sci.*, 31, 139.
Whittier, E. O., Cary, C. H., and Ellis, N. R. (1935). *J. Nutrit.*, 9, 521.

THE BIOLOGICAL ASPECT IN TREATMENT OF THE INFERTILE MARRIAGE

BY

R. CHRISTIE BROWN, M.S., F.R.C.S., F.R.C.O.G.

Honorary Surgeon, Samaritan Hospital for Women; Obstetric Surgeon, City of London Maternity Hospital

At the present day, when so many women seek advice with reference to the infertility of their marriages and so much investigation is carried out in an attempt to elucidate the causes, the criticism might be offered that most of our energies are spent in investigation and little in treatment. Nevertheless, many of our lines of investigation seem to have a direct curative value—as, for example, it would appear to be established that the performance of a tubal patency test has a curative as well as a diagnostic value: Green-Armytage (1943) has recorded a 43% success rate following the simple process of salpingography. It is not clear how this process achieves these results, but speculation upon figures quoted suggests that there is a direct relationship between the two. So many cases of immediate pregnancy following upon the simple procedure of endometrial biopsy have been reported that it is impossible to avoid the conclusion that here also the results are not merely accidental.

Reviewing treatment from the time-honoured method of dilatation of the cervix and curettage to the present-day methods of demonstrating tubal patency (salpingography and insufflation) and the surgical procedures of salpingostomy, it is at once apparent that most of our means of approach are mechanical. This is what might be expected in the present mechanical age and from the fact that the problem of the infertile marriage occupies the minds of surgeons rather than physicians.

Now that the role of the hormones of human gestation is becoming clearer and the endocrinologists are turning their attention to the problem, it is likely that the pendulum will swing a little away from the mechanical aspect towards the medical and biological side.

Four Important Questions

In investigating an infertile marriage we are concerned with four major questions: (1) The husband, his potency and the quality of his semen. (2) Ovulation. (3) The pathway which the sperms traverse to reach the ovum; and here we may consider two subdivisions—(a) the cervix and the influence of its secretions on sperm migration; (b) the Fallopian tubes. (4) Nidation or embedding of the ovum. In my opinion, the importance of nidation of the ovum has not been sufficiently stressed, and treatment based upon the assumption that many cases of infertility result from difficulty experienced by the ovum in embedding itself in the endometrium has proved to be successful in an appreciable number of my cases.

Since treatment based on the assumption of faulty nidation is purely medical and can be carried out with little inconvenience to the patient, it has gradually become my practice of recent years to initiate medical treatment aimed at securing firm implantation of the ovum in practically every patient who consults me with reference to infertility and in whom there is no gross pathology. Medical treatment can be undertaken while the patient is awaiting the propitious moment for such tests as the post-coital test, endometrial biopsy, and the tubal patency test and while the husband is being investigated by a seminologist.

Under such treatment it is surprising how often the completion of these tests is not necessary because the patient has become pregnant in the interim. Occasionally, of course, at the first examination one finds some definite and likely cause for infertility which calls for specific treatment, but more frequently no gross cause is discovered. In these latter cases treatment aimed at securing firm nidation can be started at once. In most of the patients nowadays, apart from performing a post-coital test, I like to give a trial period of two or three months under medical treatment before further investigations are undertaken.

Most authorities agree that the ovum, after fertilization, takes several days to traverse the Fallopian tubes and reach the uterus, the endometrium of which should be prepared to receive it—that is, it should be in the secretory phase, having responded to the hormones elaborated by the corpus luteum. An extended experience of endometrial biopsies taken just before the onset of a period has led me, however, to appreciate that all endometria do not show the same degree of preparation. Whether this is due to a deficient action of the corpus luteum or, as Bourne (1947) suggests, to lack of a receptive factor in the endometrium rendering it unresponsive to a normal hormonal stimulus must await further work on the subject. The fact remains that a good number of women produce an endometrium which, by our gross methods of assessment, would appear to be inadequately prepared as a nesting-ground for the fertilized egg.

A Plan of Treatment

Basing treatment upon this evidence, I advise my patients to adopt the following plan:

1. To concentrate intercourse on their fertile dates, which can be calculated for them either mathematically as occurring on the 16th, 15th, or 14th day prior to the anticipated onset of a period (in a woman with a 28-day cycle these days will be the 12th, 13th, and 14th days from the first day of the last period), or, more accurately, by instructing them to assess the days by the early-morning temperature method.

2. To abstain from intercourse for a week or ten days prior to these fertile days, which in practice amounts to abstaining from the first day of a period until the fertile days.

3. To take from the first fertile day 0.6 mg. of "dienoestrol" and 10 mg. of "ethisterone" daily.

4. To continue to take these hormones until the onset of the next period, when they are discontinued, since obviously the onset of a period indicates that on this occasion the attempt to aid nidation has failed. Should the period not start, the patients continue with these hormones daily until the 18th week of the pregnancy.

It should be noted that the administration of these hormones may delay the onset of the period by a few days even in the absence of pregnancy, but not longer. I quote the results of this treatment in 111 patients, in not one of whom could I discover any apparent cause for infertility by ordinary clinical examination. All of them had been sterile for more than two years, and 87 of them for periods varying between 3 and 10 years.

TABLE I.—Cases in which there had been no Previous Pregnancies

Total number of cases	111
Failures	73 (65.8%)
Successes	38 (34.2%)
Analysis of failures:	
Certain failures	37
No reply to letters of inquiry	36
Analysis of successes:	
Pregnant in one month	13 (11.7%)
" " two months	4 (3.6%)
" " three months	6 (5.4%)
" " six months	15 (13.5%)
Number of miscarriages	3

It will be seen that within six months, to my knowledge, on medical treatment alone, 38 (34.2%) patients had become

pregnant. Three of these patients miscarried, but all the others gave birth to live babies.

Since this line of treatment can obviously have no influence upon obstructed tubes, it is not worth trying for more than a few months. I maintain, however, that it can influence the marriage which is sterile on account of poor spermatogenesis, as I shall attempt to show, and it is particularly useful in those patients who suffer from repeated miscarriages. Table II shows the results of the analysis of 38 cases in which there had been no difficulty in conceiving but merely in retaining the foetus. Not one of the patients whose records are shown in the Table had suffered from less than two miscarriages and not one had carried a baby to term.

This method of treatment has thus a wider application, particularly in two types of case—namely, (1) cases of repeated miscarriages; (2) cases in which a fault in the husband's semen is responsible for the infertility.

Cases of Repeated Miscarriages

Many of such miscarriages appear to result from faulty nidation due either to a poorly prepared endometrium—that is, a fault in the environment—or to what can be described as poor germ-plasm—namely, a fault in the embryo. In fact, all causes of miscarriage must fall within these two categories, since Nature and Nurture, operating together, fashion the foetus—that is, embryonic development depends upon the interplay between genetic factors and factors imposed upon it by environment. A fault in either may result in impaired development or death of the embryo.

Many environmental causes of miscarriage are obvious and well known—for example, diseases of the maternal organism such as nephritis, hypertension, virus infections, etc. On the other hand, it is not so generally realized that inadequate endometrial preparation for nidation must be regarded as forming an adverse environment for the growth of the embryo, and thus it can be considered to be one of the environmental causes of miscarriage. This conclusion, however, is complicated by the fact that although the suitability or otherwise of the endometrium for nidation in the first instance is imposed upon the foetus—that is, it depends upon the activity of the corpus luteum—this is true only up to the moment of nidation, since from then onwards the continued activity of the corpus luteum and consequently the character of the endometrium depend upon a stimulus from the embryo itself. There is therefore a direct link between the genetical composition of the embryo and the continuation of the life of the corpus luteum.

Nature has in this way cunningly contrived that the intra-uterine environment shall be genetically determined, and has imposed upon the embryo the necessity to plough its own furrow.

This linkage between genetics and environment brings into consideration the father's contribution, and apportions to him part of the responsibility of ensuring an adequacy of the pregnancy hormones. The evidence obtained from the assessment of pregnanediol excretion rates suggests that a weak embryo means a weak stimulus (chorionic prolactin), and a weak stimulus a deficiency of the ovarian hormones, with a resulting poor environment and probable death and expulsion of the foetus.

Whether or not a fault in nidation is genetic (that is, a fault in the ovum) or environmental, a better environment—namely, a better-prepared endometrium—may make all the difference between success and failure. Just as in dealing with a delicate seed the husbandman prepares his soil carefully, so in order to facilitate the growth of the human ovum we should see that the endometrial soil is well

prepared before the seed is sown; and this can best be achieved by the administration of the pregnancy hormones (oestrin and progesterone) from the day of ovulation and consequently before it is known whether the patient is pregnant or not.

Below, Table II shows the results of treatment of 38 cases of repeated miscarriage, for none of which was any apparent cause found. In all these cases rhesus incompatibility was excluded. It is a point of interest that in 30 of these cases the seminologist reported that the semen was subfertile, but, since it appears to me that seminologists have no normal standard on which to base such decisions, I do not think that any accurate conclusion regarding the semen can be drawn from these reports.

TABLE II.—*Repeated Miscarriages*

Total number of cases analysed	..	..	..	38
Number pregnant in 6 months	..	..	..	28
Live births	..	..	20	
Miscarriages	..	..	6	
Stillbirths	..	..	1	
Spina bifida	..	..	1	
Number not pregnant in 6 months	..	..	..	10
Previous miscarriages (96) among the 38 patients:				
26 had had 2 miscarriages	..	..	..	52
8 " " 3 " "	..	..	..	24
4 " " 5 " "	..	..	..	20

Results According to Number of Miscarriages

Two miscarriages:				
Cases	..	..	..	26
Pregnant in 6 months	..	..	..	20
Living children	..	..	15	
Miscarriages	..	..	5	
Three miscarriages:				
Cases	..	..	..	8
Pregnant in 6 months	..	..	..	6
Living children	..	..	4	
Miscarriages	..	..	1	
Spina bifida	..	..	1	
Five miscarriages:				
Cases	..	..	..	4
Pregnant in 6 months	..	..	..	2
Living child	..	..	1	
Stillbirth at 8 months	..	..	1	

Thus in six months 28 of these 38 patients were pregnant and 20 carried their babies through to term. Two were delivered by caesarean section.

Infertility due to Inadequate Semen

Where we are dealing with a case of infertility in which we know that the semen is inadequate the same argument of preparing the soil to compensate for genetic weakness of the seed holds good.

Finally, there are two points in this plan which I would like to emphasize:

1. It has been shown by Allen (1932) and Leonard, Hisaw, and Fevold (1932) that progesterone proliferation of the endometrium will not take place unless it has been first sensitized by oestrin. It is for this reason that dienoestrol is administered in conjunction with ethisterone (progesterone). Also, it may be that the varying endometrial changes sometimes seen are due to an imbalance of these two hormones—that is, the endometrial response to progesterone is poor because there is not present at the same time an adequate oestrogenic secretion.

2. The hormonal treatment is continued until the 18th week and then withdrawn, since it has been shown by Browne, Henry, and Venning (1939) and others that there is a sharp rise in pregnanediol excretion about the 13th to the 16th week, and this increased excretion has been interpreted as signifying the commencement of elaboration of progesterone by the foetal chorion.

To continue to boost a pregnancy after this time, apart from being difficult and expensive, would appear to be eugenically unsound, since, if the foetus cannot elaborate enough hormones for the continuation of the mother's pregnancy, it might be a dysgenic act to allow it to live. Malpas (1942), Wenner (1941), and others have drawn attention to the fact that the incidence of foetal malformations is closely bound up with the problem of miscarriage,

and Wenner states that if a threatened miscarriage continues to term there is a greater than average chance of a deformed baby resulting.

During the recent war I was tempted on three occasions to give larger quantities of the ovarian hormones than is my custom and to continue them throughout the whole of the pregnancy. These three patients had threatened to miscarry before I saw them, and were bleeding when I first examined them, although uterine contractions were absent and urine pregnancy tests were positive. All three continued to bleed from time to time throughout the pregnancy, uterine growth was poor, and the breasts lacked serum.

After treatment of such patients for a week or two I would normally have withdrawn the hormones and allowed the miscarriages to take place. These three patients, however, were elderly primigravidae, and their husbands were going on service abroad and were not likely to return in time to make further conception possible. I therefore continued to administer large quantities of hormones throughout the pregnancies in spite of repeated bleedings, slowly growing hard uteri, and poor breast changes. All three terminated their pregnancies by premature labour between the 30th and 35th weeks, and all three gave birth to abnormal babies, not one of whom survived. Two of the babies were cases of exomphalos and one was a case of microcephaly, and the labour was accompanied by bleeding from a placenta praevia.

I therefore now discontinue administering the hormones at the 18th week, at which time the function of the corpus luteum is over and the hormones should have been elaborated entirely by the embryo itself. The embryo should, as it were, stand on its own feet from then onwards.

To continue to treat a case of threatened miscarriage in spite of repeated bleedings can be likened to watering a garden when a plant is withering. The damage has already probably been done and we are unaware of the direction in which the embryo is developing. In most cases it would be advisable to allow the miscarriage to complete itself and start again with an endometrium adequately prepared—that is, to sow the seed in better soil by adopting the plan which I have outlined above—since a good start means good roots and good roots a good superstructure (the foetus). For this reason it does not appear to me to be unwise to aid the embedding and early growth of the embryo, but once the stage is reached at which large quantities of hormones are necessary and at which they are elaborated entirely by the foetal chorion I think that in the interest of eugenics the help should be withdrawn.

Embryos of all animals lower than the mammals have a very uncertain environment, for which they are compensated by multi-egg spawning. The environment of the mammalian embryo, however, is so potentially safe that were some check not placed upon it many abnormalities might survive. Nature, however, has determined that mammalian embryonic environment shall be genetically controlled, and thus those embryos which fail to elaborate enough hormones for their own survival are discarded. In the present state of our knowledge of embryonic growth it would seem to be unwise to run counter to this principle.

REFERENCES

- Allen, W. M. (1932). *Amer. J. Physiol.*, **100**, 650.
 Bourne, Aleck (1947). *British Medical Journal*, **1**, 79.
 Browne, J. S. L., Henry, J. S., and Venning, E. H. (1939). *Amer. J. Obstet. Gynec.*, **38**, 927.
 Green-Armytage, V. B. (1943). *J. Obstet. Gynaec. Brit. Emp.*, **50**, 23.
 Leonard, S. L., Hisaw, F. L., and Fevold, H. L. (1932). *Amer. J. Physiol.*, **100**, 111.
 Malpas, Percy (1942). *J. Obstet. Gynaec. Brit. Emp.*, **49**, 65.
 Wenner, R. (1941). *Mtschr. Geburtsh. Gynäk.*, **112**, 325.